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(54) Title: SENSOR SYSTEM WITH A REFERENCE SURFACE MIMICKING THE DETECTION SURFACE BUT WITH LOW LIGAND BINDING CAPACITY

(57) Abstract: The invention concerns a sensor system with at least two flexible units, a sensor unit and a reference unit. The sensor unit comprises a capture surface area functionalised by linking one or more functional groups comprising a capture ligand, such as a member of a specific binding pair. The reference unit comprises an imitated capture surface area which area has been functionalised by linking one or more functional groups, wherein said one or more functional groups linked to the imitated capture surface area of said reference unit do not include a ligand which is identical with said capture ligand. The capture ligand may e.g. be a specific binding partner for a biocomponent, preferably selected from the group consisting of RNA oligos, DNA oligos, PNA oligos, protein, peptides, hormones, blood components, antigen and antibodies. The sensor unit and the method make it possible to reduce the noise, because the signal obtained from the reference unit which is measuring the noise may be subtracted from a signal obtained from the sensor unit.

SENSOR SYSTEM WITH A REFERENCE SURFACE MIMICKING THE DETECTION SURFACE BUT WITH LOW LIGAND BINDING CAPACITY

The present invention relates to a sensor system for detecting the presence or the amount of a substance e.g. a target biocomponent in a fluid such as a liquid.

Bagground of the invention

It is known from e.g. WO 0066266 and WO 9938007 that micro-cantilevers can be used for detection of molecular interaction. Capture molecules are immobilised on the surface of the cantilever. When the capture molecules bind to an analyte in the sample that is presented to the cantilever, this will induce a change in the surface stress of the cantilever, and consequently the cantilever will deflect and/or stretch.

Measuring the reflection angle from a laser beam that is directed to the cantilever can detect a deflection. Another sensor principle is the use of a piezoresistor integrated into the cantilever. In this detection principle the deflection/stretch is detected as a change in the electrical resistance of the piezoresistor.

The signal from the measuring cantilever comprises both the signal from the deflection and stretch of the cantilever but also from noise.

It has previously been demonstrated that a blank cantilever can be coupled e.g. in a Wheatstones bridge with the measuring cantilever in order to eliminate the mechanical noise in the system which may include, but is not limited to, external vibration, temperature changes etc.

In this case the signal from the reference cantilever can be described as:

[2] $$S_{ref} = S_{mech.\ noise}$$

where:
Sref = Total signal from the reference cantilever

The noise of the signal has thereby been reduced significantly. However, the signal measured still includes noise, and it is the object of the present invention to provide a sensor system where the amount of noise is even further reduced than in the prior art solutions described above.

Summary of the invention

It has been found that the signal from the measuring cantilever will be a combination of several components:

[1] $$S_{mc} = S_{spec.bind.} + S_{mech.\ noise} + S_{unspec.\ bind.}$$

where:
S_{mc} = Total signal from the measuring cantilever
$S_{spec.bind.}$ = Signal due to the specific binding of the analyte to capture molecules
$S_{mech.\ noise}$ = Signal due to mechanical noise, e.g. external vibrations, temperature variation
$S_{unspec.\ bind.}$ = Signal from unspecific binding of molecules in the sample to the capture molecules

Unspecific binding is a substantial problem in all binding assays as it is impossible today to distinguish between specific and unspecific binding. As can be seen the formulas above and the use of a traditional reference cantilever do not eliminate this problem.

The objective of the invention is therefore to provide a sensor system which system does not have the drawbacks as described above. The invention as it is defined in the claims provides a sensor system with a reduced level of noise compared to prior art sensors.

The sensor system according to the invention comprises at least two flexible units, wherein one of said units is ``a sensor unit'' and another one is ``a reference unit''. The sensor unit comprises a capture surface area which area has been functionalised by linking one or more functional groups comprising a capture ligand to said capture surface area.

The reference unit comprises an imitated capture surface area, which area has been functionalised by linking, preferably covalently linking one or more functional groups. The reference unit differs from the sensor unit in the composition of the functional groups linked to its surface. As it will be clear from the following, the main issue of the invention is that the reference unit is functionalised but that it contains less or no functional groups which are identical with the capture ligand of the sensor unit. In one embodiment, the imitated surface area contains no or less members of the specific binding pair which is complementary to the same binding partner member as the capture ligand of the sensor unit.

Disclosure of the invention

The sensor system of the invention concerns a set-up as defined in the claims which system comprises a measuring sensor unit which is coupled to an ``intelligent'' reference unit. In this set-up it has surprisingly turned out that the reference unit can be used to partly or totally eliminate not only mechanical noise, but also to reduce or eliminate the noise originating from unspecific binding.

The sensor unit is functionalised by immobilising capture molecules as normally to a capture surface area of the sensor unit. Contrary to the normal procedure, the reference unit is also functionalised at a surface area designated ``an imitated capture surface area''.

In one embodiment the noise is reduced significantly, e.g. to 50 % or lower compared to prior art technology.

In one embodiment, the noise resulting from unspecific binding is essentially eliminated i.e. within measuring uncertainty.

In the following the term ``a ligand'' means a type of ligand, and similarly ``a binding partner'' means a type of binding partner and so on.

Both the capture surface area (which means the capture surface area of the sensor unit), and the imitated capture surface area (which means the imitated capture surface are of the reference unit) are functionalised by linking one or more functional groups to the surfaces, preferably so that the amount of proteins, amino acids and/or lipids that binds via unspecific binding to the imitated capture surface area is closer to the amount of

similar components that binds via unspecific binding to the capture surface area than if the reference unit was not functionalised.

The functional groups linked to the capture surface area and the reference surface area, respectively, may be linked chemically e.g. covalently or ionic bondings; or physically. In one embodiment, one or more of the functional groups are linked via covalent bonds. In one embodiment, one or more of the functional groups are linked by adsorption. Adsorption means a non-specific physical interaction between the functional groups and the surface area. Adsorption is relatively cheap, easily carried out, and tends to be less disruptive to enzymic proteins than chemical means of attachment, the adsorption binding being mainly by hydrogen bonds, multiple salt linkages, and Van der Waal's forces. Adsorption bears the greatest similarity to the situation found in biological membranes in vivo and may therefore in some embodiments be preferred.

The size of the sensor unit capture surface area and the size of the reference unit imitated surface area may differ from each other or it may be equal. If the size of the sensor unit capture surface area and the size of the reference unit are equal to each other, the calculation of the signal with reduced or no noise is easier than if the sizes differ from each other. In the latter case, a correlation factor compensating for the size difference should be implemented.

The capture ligand is a member of a specific binding pair. Such ligands which is members of a specific binding pair is well known in the art, and further, information concerning such binding pair can be found in WO 0066266,

WO 9938007, US 5,156,810, WO 0036419 and WO 9631557 which publication are hereby incorporated by reference.

By the term specific bonding pair is meant any pair of target molecule/capture ligand with an ability to specifically bind to one another e.g. receptor/target ligand, enzyme/substrate (or analogue), nucleic acid binding protein/nucleic acid etc. Such specific bonding pair of target molecule/capture ligand is thereby said to be complementary to each other.

In one embodiment, the binding pair in the form of the capture ligand binding partner and a target binding partner is selected among antigen-antibodies or fragments thereof and nucleic acid strands - nucleic acid strands.

In one embodiment, a molecule that shows similarity to the capture molecules is immobilised to the reference unit. The molecules on the reference unit though, in this embodiment do not exhibit a specific binding to the analyte that the assay is designed to detect.

In one embodiment, the one or more functional groups linked to the imitated capture surface area of the reference unit do not include a ligand, which is identical with the capture ligand. In one embodiment, the one or more functional groups linked to the surface area of said reference unit do not include a ligand which is a member of the specific binding pair.

The molecules on the reference unit can belong to any class of molecules and do not necessarily have to be of the same class as the molecules on the sensor unit.

In one embodiment, the functional group linked to the imitated surface area of the reference unit includes a

reference ligand. The reference ligand may in one embodiment be present in a number which is 50 % or more such as 75 % or more, such as 90 % or more of the number of capture ligands on the capture surface of the sensor unit. In one embodiment, the reference ligand is of the same chemical class as the capture ligand of the sensor unit. The chemical class may e.g. be one of a) nucleic acids and strands thereof such as DNA oligos, PNA oligos, RNA oligos; b) proteins including peptides, antigen, antibodies and hormones; and c) lipids.

In one embodiment of the sensor system according to the invention, the sensor system is directed to detecting the presence of a preselected target biocomponent. The sensor unit comprises a capture surface area which area has been functionalised by linking a capture ligand, where said capture ligand is a capture ligand for the preselected target biocomponent. The reference unit comprises an imitated capture surface area which area has been functionalised by linking one or more functional groups, wherein the one or more functional groups of the imitated capture surface have less tendency to bind to the preselected target biocomponent than the capture ligand. In one embodiment, the functional groups linked to said imitated capture surface area of said reference unit do not include a ligand, which is a capture ligand for said preselected target biocomponent.

In one embodiment, the amount of proteins, amino acids and/or lipids that binds via unspecific binding to the imitated capture surface area is 50 % or more, such as 60 % or more, such as 70 % or more, such as 80 % or more, such as 90 % or more, such as essentially the same as the amount of similar components that binds via unspecific binding to the capture surface area. In one embodiment, this is measured by using DAKO Human Serum Protein

Calibrator as test medium. In one embodiment, this is measured by using DAKO Lipoprotein (a) Calibrator as test medium.

When a sample is presented to the sensor unit and reference unit, the analyte, which is a binding partner to the capture ligand (if present), will bind to the capture ligand on the sensor unit. Also various other molecules in the sample will unspecifically bind to the functional groups on the sensor unit.

In one embodiment, it is desired that the one or more functional groups of the imitated capture surface have a capture tendency of 50 % or less, such as 40 % or less, such as 30 % or less, such as 20 % or less, such as 10 % or less than the capture tendency of the capture ligand toward said preselected target biocomponent.

In one embodiment, the reference ligand of the reference unit has essentially the same charge as the capture ligand of at least one sensor unit connected to the reference unit. Essentially the same charge means that the charge of the respective capture/reference ligands differs from each other by 10 % or less, preferably by 5 % or less measured in water.

In one embodiment, the imitated capture surface area of the reference unit has essentially the same pH value as the capture surface area of at least one sensor unit connected to the reference unit. Essentially the same pH value means that the pH value of the respective surface areas differs from each other by 0.5 pH or less, preferably by 0.1 pH % or less measured in water.

In one embodiment, the reference ligand of the reference unit has essentially the same hydrophility as the capture ligand of the sensor unit.

In one embodiment, the reference ligand of the reference unit has essentially the same structure as the capture ligand except for the binding site or sites, which may e.g. be blocked, removed or replaced by non-active chemical group(s).

In one embodiment, the imitated capture surface area of the reference unit has a surface tension measured as contact angle to a water droplet which is the same + - 2 ° as the surface tension of the capture surface area of the sensor unit.

In one embodiment of the sensor system of the invention the capture ligand is present in a first concentration linked to the capture surface area, and the capture ligand linked to the imitated capture surface area in a second concentration, wherein said second concentration is substantially less than the first concentration such as 50 % or less, such as 40 % or less, such as 30 % or less, such as 20 % or less, such as 10 % or less than the first concentration. In this embodiment also a part of the signal originating from a bonding between capture ligand and target ligand will be suppressed, this effect may therefore further be used in determining concentrations of a target biocomponent in a sample.

In one embodiment, it is desired that the sensor system according to the invention comprises one or more sensor units and one or more reference units, where at least one, preferably each of the sensor units, is connected to at least one reference unit. The connection may preferably include a coupling of the connected sensor

unit and reference unit so that a signal obtained from the reference unit is subtracted from a signal obtained from the sensor unit, more preferably said sensor unit and said reference unit being coupled in a Wheatstones bridge.

The sensor and the reference units are coupled in a way so that the signal from the reference unit (e.g. a cantilever) is subtracted from the signal from the sensor unit (e.g. a cantilever). This could be done by coupling them in a Wheatstones bridge in the same way as described in WO 0066266 and disclosed in WO 0066266 FIG. 3, the figure and accompanying description hereby being incorporated by reference.

The sensor system according to the invention may in principle comprise an unlimited number of sensor units and reference units, and the invention includes embodiments wherein two or more sensor units are coupled to one reference unit, and embodiments wherein two or more reference units are coupled to one sensor units. The sensor system may preferably include two or more sensor unit, preferably at least 5 sensor units, more preferably at least 10 sensor units, wherein each of said sensor units preferably comprises a capture surface area which area has been functionalised by linking, preferably by adsorption linking one or more functional groups comprising a capture ligand to said capture surface area, the capture ligand linked to each sensor units being a member of a specific binding pair. In one embodiment, the capture ligand on one sensor unit preferably is different from the capture ligand of another sensor unit. Thereby several specific target molecules may be detected by the sensor system simultaneously.

In one embodiment, at least one sensor unit and at least one reference unit, which are preferably coupled, have substantially the same size. ``Substantially the same size'' means within a 10 % variation based on the largest of the sensor/reference units. In one embodiment, ``substantially the same size'' means within a 5 % variation based on the largest of the sensor/reference units.

In one embodiment of the system according to the invention, the sensor unit(s) and the reference unit(s), which are coupled together, and preferably all of the sensor units and the reference units may preferably have substantially identical shapes.

In one embodiment, at least one reference unit coupled to a sensor unit has a thickness which is identical +- 10 % of the thickness of the sensor unit.

In one embodiment, the capture surface area and imitated capture surface area of pair wise sensor/reference flexible units have substantially identical sizes, wherein ``substantially identical'' should mean within a difference of 20 %, preferably within a difference of 10 %, even more preferably within a difference of about 5 %.

The flexible unit may in principle have any shape. In one embodiment, the flexible unit or a part of the unit is sufficiently flexible to perform a measurable change due to a stress reaction on the capture surface area/imitated capture surface area when the analytes or substances to be detected are adsorbed or linked to the capture surface area. In one embodiment, the flexible unit should have a free flexing area which is not directly bonded to a solid material.

In one embodiment, the flexible units comprise one or more units selected from the group consisting of cantilevers, bridges and membranes. In one embodiment, the flexible units are of micro size, which means that the flexible units have dimensions which are 500x500x500 μm or less, preferably 5x100x200 μm or less. The shape of the flexible units may e.g. be as described in US 6016686 WO 0066266.

In one embodiment, the flexible units comprise a piezoresistor by use of which it is possible to register change in stress of the capture surface area. Further information concerning this aspect can also be found in WO 0066266, which information is hereby incorporated by reference.

The ligand linked to the sensor unit may preferably be linked via a spacer. Information concerning useful spacer molecules can be found in WO 9631557.

In one embodiment, the capture ligand is selected from the group consisting of RNA oligos, DNA oligos, PNA oligos, protein, peptides, hormones, blood components, antigen and antibodies.

In one embodiment, the capture ligand is a specific binding partner for a biocomponent, preferably selected from the group consisting of RNA oligos, DNA oligos, PNA oligos, protein, peptides, hormones, blood components, antigen and antibodies.

The term biocomponent further includes biomolecules and biocomponents selected from the group consisting of tissue, cells, body fluids, blood components, microorganism, derivatives thereof, or parts thereof.

The term biomolecule includes molecules of microbial, plant, animal, viral, fungal or human origin or synthetic molecules resembling them, preferably selected from the group consisting of proteins, glyco proteins, nucleic acids, such as RNA, DNA including cDNA, PNA, LNA, oligonucleotides, peptides, hormones, antigens, antibodies, lipids, sugars, carbohydrates, and complexes including one or more of these molecules, said biomolecule or molecules preferably being selected from the group consisting of nucleic acids, lipids, antibodies, proteins and protein complexes.

According to an embodiment of the invention the functional groups linked to the sensor unit capture surface area may further comprise one or more components selected from the group consisting of carboxylic acids, esters, acid halides, aldehydes, ketons, alcohols, thiols, disulphides, amins, ethers, halides, hydrazines and saccharides. These one or more components linked to the sensor units may preferably also be linked to the imitated capture surface area of a reference unit connected to the sensor unit.

In one embodiment, the functional groups linked to the reference unit imitated capture surface area comprise one or more components selected from the group consisting of carboxylic acids, esters, acid halides, aldehydes, ketons, alcohols, thiols, disulphides, amins, ethers, halides, hydrazines and saccharides.

Also according to an embodiment of the invention it is preferred that the functional groups linked to the reference unit imitated capture surface area further comprise one or more reference ligands. In one embodiment, the reference ligand is covalently linked to said imitated capture surface area of the reference unit,

optionally via a spacer. In another embodiment, the reference unit is adhered to said imitated capture surface area. The reference ligand may e.g. be selected from the group consisting of RNA oligos, DNA oligos, PNA oligos, protein, peptides, hormones, blood components, antigen and antibodies, wherein said reference ligand is different from the capture ligand of a sensor unit connected to said reference unit.

In one embodiment, the flexible units may be driven by an actuator e.g. comprising a piezoelectric element.

In one embodiment, the flexible units each comprise a piezoresistor by use of which it is possible to register change in stress of the (imitated) capture surface area.

In one embodiment, the sensor unit comprises one or more interaction chambers, e.g. as described in WO 0066266. In this embodiment the (imitated) capture surface(s) should be exposed partly or totally to a liquid in at least one interaction chamber.

In one embodiment, it is desired that the size of the interaction chamber or chambers differs individually from each other by a volume of up to about 1 ml, such as up to about 0.1 ml, such as up to about 0.05 ml such as up to about 1 µl. By using a small interaction chamber, a laminar flow of the test sample may be provided in the chamber, which may also reduce or even eliminate noise originating from turbulence.

In one embodiment, the sensor unit comprises one or more channels for introducing the sample. In this embodiment it is desired that the (imitated) capture surface(s) should be exposed to a liquid in at least one channel. In one embodiment it is desired that the cross dimensions of

the channel should be sufficiently small to provide for a laminar flow of a liquid sample through the channel. The channel(s) may e.g. have a cross sectional dimension of up to 250000 μm^2, such as up to 100000 μm^2, such as up to 25000 μm^2, such as up to 2500 μm^2.

The sensor system may e.g. be produced as disclosed in ``atomic force microscopy probe with piezoresistive read-out and highly symmetrical Wheatstones bridge arrangement'' Sensors and Actuators 83 (2000) 47-53 by Jacob Taysen et al. and WP 00662266, with the difference that the sensor system is modified according to the claims whereby the sensor unit and the reference unit are functionalised as described above.

Example 1

A sensor and reference unit shaped as cantilevers are prepared with a gold surface for immobilising a ligand in the form of capture/reference ligands to the surface. A first thiol-modified-DNA oligo (the capture oligo) is immobilised to the sensor gold cantilever surface using an Au - S bond.

A second thiol-modified-DNA oligo (the reference oligo) is immobilised to the reference cantilever. The reference oligo is chosen so the sequence does not resemble any known or expected sequence in the sample to be analysed.

Sample is presented to the assay and specific hybridisation will occur between the capture oligo and DNA in the sample, if the counterpart of the capture oligo is present in the sample.

Other molecules present in the sample will at the same time unspecifically bind to the capture oligo. This

effect expressed as a signal is eliminated by the reference oligo, where unspecific binding of the same order also takes place. The effect of the unspecific binding to the capture oligos is eliminated by the use of the reference cantilever.

Example 2

Sensor and a reference unit shaped as cantilevers are prepared with a gold surface for immobilising ligands in the form of capture/reference ligands to the surfaces.

An aptimer is immobilised to the surface of the sensor cantilever using a thiol-modified spacer.

On the reference cantilever a similar thiol-modified spacer (without the aptimer) is immobilised, at the same density as at the sensor cantilever.

Sample is presented to the assay and specific binding will occur between the aptimer and analyte in the sample, if the counterpart of the aptimer is present in the sample.

Other molecules present in the sample will at the same time unspecifically bind to the aptimer and the spacer on the measuring cantilever. The effect of the unspecific binding is partially eliminated by the reference cantilever, where unspecific binding to the immobilised spacer also takes place.

Example 3

A sensor and a reference unit shaped as cantilevers are prepared for immobilising a capture ligand and a reference ligand, respectively. A first capture ligand is

immobilised on the surface of the sensor cantilever using adsorption. The first capture molecule is for example Rabbit Anti-Human CRP.

A reference ligand is immobilised on the reference cantilever. The second capture molecule is for example Human Anti-Rabbit IgG. The reference capture molecule is chosen such that it shows minimal interaction with the capture ligand.

Sample is presented to the assay and specific recognition will occur between the capture ligand on the detection cantilever and its complementary target binding partner, if the target binding partner is present in the sample.

Other molecules present in the sample will at the same time bind unspecifically to the sensor cantilever. This effect is reduced by the reference cantilever where unspecific binding of the same order also takes place.

PATENT CLAIMS

1. A sensor system comprising at least two flexible units, one of said units being a sensor unit and comprising a capture surface area, which area has been functionalised by linking one or more functional groups comprising a capture ligand to said capture surface area, said capture ligand being a member of a specific binding pair, another one of said flexible units being a reference unit and comprising an imitated capture surface area which area has been functionalised by linking one or more functional groups, wherein said one or more functional groups linked to the imitated capture surface area of said reference unit do not include a ligand which is identical with said capture ligand, preferably said one or more functional groups linked to the surface area of said reference unit do not include a ligand which is a member of said specific binding pair.

2. A sensor system according to claim 1, wherein said capture ligand is a specific binding partner for a biocomponent, preferably selected from the group consisting of RNA oligos, DNA oligos, PNA oligos, protein, peptides, hormones, blood components, antigen and antibodies.

3. A sensor system according to any one of the claims 1 and 2, said system comprising one or more sensor units and one or more reference units, each sensor unit being connected to at least one reference unit, said connection preferably including a coupling of the connected sensor unit and reference unit so that a signal obtained from the reference unit is subtracted from a signal obtained from the sensor unit, more preferably said sensor unit

and said reference unit being coupled in a Wheatstones bridge.

4. A sensor system according to any one of the preceding claims wherein said sensor system comprises two or more sensor units, preferably at least 5 sensor units, more preferably at least 10 sensor units, each of said sensor units preferably comprising a capture surface area which area has been functionalised by linking one or more functional groups comprising a capture ligand to said capture surface area, the capture ligand(s) of one or more sensor units being a member of a specific binding pair, preferably the capture ligand on one sensor unit being different from the capture ligand of another sensor unit, more preferably the capture ligand of one sensor unit being a binding partner for a different target binding partner than the capture ligand of another sensor unit.

5. A system according to any one of the preceding claims wherein the sensor unit(s) and the reference unit(s) which are coupled together, and preferably all of the sensor units and the reference units have essentially identical shapes, preferably the imitated capture surface area/ capture surface area of all the flexible units have essentially identical sizes.

6. A system according to any one of the preceding claims wherein the flexible units are selected from the group consisting of cantilevers, bridges and membranes, said flexible units preferably being of micro size, which means that the flexible units have dimensions which are less than 500x500x500 μm, preferably less than 5x100x200 μm.

7. A system according to any one of the preceding claims wherein said flexible units each comprise a piezoresistor by use of which it is possible to register change in stress of the capture surface area.

8. A system according to any one of the preceding claims wherein said capture ligand is linked to said capture surface area of the sensor unit, optionally linked via a spacer, said capture ligand being selected from the group consisting of RNA oligos, DNA oligos, PNA oligos, protein, peptides, hormones, blood components, antigen and antibodies.

9. A system according to any one of the preceding claims wherein said functional groups linked to said sensor unit capture surface area further comprise one or more components selected from the group consisting of carboxylic acids, esters, acid halides, aldehydes, ketons, alcohols, thiols, disulphides, amins, ethers, halides, hydrazines and saccharides, said one or more components preferably also being linked to the imitated capture surface area of a reference unit connected to the sensor unit.

10. A system according to any one of the preceding claims wherein said functional groups linked to said reference unit imitated capture surface area comprise one or more components selected from the group consisting of carboxylic acids, esters, acid halides, aldehydes, ketons, alcohols, thiols, disulphides, amins, ethers, halides, hydrazines and saccharides.

11. A system according to any one of the preceding claims wherein said functional groups linked to said reference unit imitated capture surface area further comprise one or more reference ligands, said reference ligand

preferably being covalently linked or linked by adsorption to said imitated capture surface area of the reference unit, optionally via a spacer, said ligand preferably being selected from the group consisting of RNA oligos, DNA oligos, PNA oligos, protein, peptides, hormones, blood components, antigen and antibodies, wherein said reference ligand is different from the capture ligand of a sensor unit connected to said reference unit.

12. A system according to claim 11 wherein said reference ligand is of the same chemical class as the capture ligand of a sensor unit connected to the reference unit, said chemical class preferably being one of a) nucleic acids and strands thereof such as DNA oligos, PNA oligos, RNA oligos; b) proteins including peptides, antigen, antibodies and hormones; and c) lipids.

13. A system according to any one of the claims 11 and 12 wherein said reference ligand of the imitated capture surface of the reference unit has essentially the same charge as the capture ligand of at least one sensor unit connected to the reference unit.

14. A system according to any one of the claims 11 and 12 wherein said imitated capture surface area of the reference unit has essentially the same pH value as the capture surface area of at least one sensor unit connected to the reference unit.

15. A system according to any one of the claims 11 and 12 wherein said reference ligand of the imitated capture surface of the reference unit has essentially the same hydrophility as the capture ligand of at least one sensor unit connected to the reference unit.

16. A system according to any one of the claims 11 and 12 wherein said reference ligand of the imitated capture surface has essentially the same structure as the capture ligand except for the binding site or sites, which may e.g. be blocked, removed or replaced by non-active chemical group(s).

17. A system according to any one of the preceding claims wherein said imitated capture surface area of the reference unit has a surface tension measured as contact angle to a water droplet which is the same + - 2 ° as the surface tension of the capture surface area of at least one sensor unit connected to the reference unit.

18. A system according to any one of the preceding claims wherein said capture ligand is selected from the group consisting of RNA oligos, DNA oligos, PNA oligos, protein, peptides, hormones, blood components, antigen and antibodies.

19. A system according to any one of the preceding claims wherein said binding pair in the form of the capture ligand binding partner and a target binding partner is selected among antigen-antibodies or fragments thereof and nucleic acid strands - nucleic acid strands.

20. A sensor system for detecting the presence of a preselected target biocomponent, said sensor system comprising at least two flexible units, one of said units being a sensor units and comprising a capture surface area which area has been functionalised by linking one or more functional groups comprising a capture ligand to said capture surface area, said capture ligand being a capture ligand for said preselected target biocomponent, another one of said flexible units being a reference unit and comprising an imitated capture surface area which

area has been functionalised by linking one or more functional groups, wherein said one or more functional groups of the imitated capture surface have less tendency to capture said preselected target biocomponent than the capture ligand, preferably said functional groups linked to said imitated capture surface area of said reference unit do not include a ligand which is a capture ligand for said preselected target biocomponent.

21. A sensor system according to claim 20, wherein said one or more functional groups of the imitated capture surface have a capture tendency of 50 % or less, such as 40 % or less, such as 30 % or less, such as 20 % or less, such as 10 % or less than the capture tendency of the capture ligand toward said preselected target biocomponent.

22. A sensor system according to any one of the claims 20 and 21, wherein said capture ligand is a specific binding partner for a biocomponent, preferably selected from the group consisting of RNA oligos, DNA oligos, PNA oligos, protein, peptides, hormones, blood components, antigen and antibodies.

23. A sensor system according to any one of the claims 20-22, said system comprising one or more sensor units and one or more reference units, each sensor unit being connected to at least one reference unit, said connection preferably includes a coupling of the connected sensor unit and reference unit so that a signal obtained from the reference unit is subtracted from a signal obtained from the sensor unit, more preferably said sensor unit and said reference unit being coupled in a Wheatstones bridge.